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The utility of genetically modified animals in modeling OCD-spectrum disorders

Amanda N. Smolinsky[1], Carisa L. Bergner[1], Peter C. Hart[1,2],

Rupert J. Egan[1], Brett D. Dufour[3], Justin L. LaPorte[1], Allan V. Kalueff [1,2,4*]

[1] Department of Physiology and Biophysics, Georgetown University Medical School, 3900 Reservoir Road, Washington, DC 20057, USA

[2] Department of Pharmacology, Tulane University Medical School, Tulane University, 1430 Tulane Avenue, New Orleans, LA 70112, USA

[3] Department of Animal Sciences, Purdue University, 915 W State St., West Lafayette, IN 47907, USA

[4] Stress Physiology and Research Center (SPaRC), Georgetown University Medical Center, 3900 Reservoir Road, Washington, DC 20057, USA

*** Corresponding Author:**

Dr. Allan V. Kalueff, PhD

Department of Physiology and Biophysics

Basic Science Building, Room 254

Georgetown University Medical School

3900 Reservoir Road, Washington, DC 20057, USA

Tel: (202) 687-4563

Email: avkalueff@gmail.com, ak523@georgetown.edu

Abstract

Obsessive-compulsive disorder (OCD) inflicts uncontrollable intrusive thoughts and ritualistic compulsive behaviors and manifests in approximately 3% of the population. Clinical symptoms of OCD can be categorized as checking, hoarding, washing, or ordering. Mounting evidence suggests that OCD phenotypes can be modeled effectively, and with remarkable validity, through translational approaches in ethological animal models. Experimental models of OCD-like behavior, including nesting, marble burying, grooming, spatial alternation, and barbering allow researchers to investigate the neurobiological mechanisms responsible for this disorder. While its exact pathogenesis remains unknown, genetic factors also play a key role in OCD. Genetic animal models of OCD and related disorders are now becoming available, aiding researchers in identifying associated neural pathways and pharmacological treatments. Here we discuss how some genetically modified animals may be used for modeling OCD-like endophenotypes.

Keywords: Obsessive-compulsive disorder, genetic animal models, behavioral perseverations

Introduction

Obsessive-compulsive disorder (OCD) affects approximately 3% of the population (Fineberg et al 2007; Graybiel and Rauch 2000), causing uncontrollable repetitive thoughts and ritualistic behaviors to assuage those thoughts (Fineberg et al 2007), Fig. 1. Patients afflicted with the disorder are often painfully aware that their thoughts and actions are irrational, but can continue to follow through with them for hours (Graybiel and Rauch 2000), resulting in shame and unwillingness to seek help that can delay diagnosis of the disorder (Heyman et al 2006). Based on the symptoms a patient presents, manifestations of OCD can be grouped into four categories, including checking, hoarding, washing, and ordering (Mataix-Cols et al 2004; Pauls et al 2002). Checking symptoms may include sexual, religious, aggressive, or somatic obsessions, accompanied by compulsions to ameliorate the obsession. Hoarding-type OCD involves obsessions and compulsions related to the stockpiling of objects. Patients with washing symptoms obsess about contamination and demonstrate washing and cleaning compulsions, whereas those with ordering-type OCD obsess over symmetry or exactness, and have rituals for repeating, counting, or arranging, actions or objects (Heyman et al 2006; Pauls et al 2002).

The Obsessive-compulsive spectrum disorders (OCSD) is a grouping of human psychiatric disorders that involve compulsive and/or impulsive symtoms (Hollander 1993; Hollander and Wong 1995). The OCSD include trichotillomania, hypochondriasis, self-harm disorders, tic disorders, body dysmorphic disorder, and eating disorders, in addition to OCD (Hollander and Wong 1995) (Fig. 1). While it is has been argued that these disorders may in fact be related to OCD, the basis for this classification is purely behavioral (i.e. the involvement of impulsive/compulsive symptoms) without necessarily having a basis in shared etiology, pathophysiology, or treatment profile. As these biological features largely remain unknown, the exact membership in the OCSD family and the classification of the entire group into anxiety disorders remain open to debate (Angst et al 2005;

Fineberg et al 2007; Richter et al 2003). Indeed, as Fineberg et al. (2007) note, "similarities in phenomenology and comorbidity rates could argue equally well for inclusion of OCD into affective disorders, psychotic disorders, and, even, addiction."

The discussion on how to classify OCD and other disorders that are potentially related has produced numerous different hypotheses regarding the proper segmentation and optimal diagnostic rubric. Many subtypes of the disorder have been proposed, even for disorders not traditionally paired to OCD, such as autism and Asperger's (Bejerot 2007). Some authors posit that typical clinical behaviors are being misdiagnosed due to an overlap in symptomology between the disorders (Bejerot et al 2001), making it less likely for the patient to receive relevant treatment. Similarly, other researchers are investigating the possibility that many of the symptoms that have been intrinsic to OCD, such as hoarding behaviors, could be reinterpreted as distinct syndromes (Pertusa et al 2008). Although there is disagreement on the specific nosology of OCD, it is understood that the examination using animal models will play a crucial role in determining the etiology of the disorder, and lead to a more sophisticated understanding of its affects through investigations of its neurophysiological substrates (see further).

Neurobiology of OCD

Overall, clinical studies suggest a heterogeneous mechanism for OCD/OCSD, involving a variety of neurochemical and genetic pathways (Hasler et al 2005; Pauls et al 2002; Richter et al 2003). Importantly, twice as many patients with OCD have a co-morbid disorder than have OCD alone (Fineberg et al 2007). Disorders commonly associated with OCD include other members of OCSD, depression, and anxiety disorders (particularly, major depressive disorder and social phobias) (Fineberg et al 2007; Heyman et al 2006). Due to the high rate of co-occurrence between OCD and OCSD, it has been suggested that they share a common genetic basis (Richter et al 2003). While

OCD can be heritable in families, as many familial and twin studies have shown, little is known about the genetic mechanisms underlying OCD (Pauls et al 2002).

The current understanding of OCD pathogenesis has implicated several brain regions. For example, abnormal metabolic activity has been observed in OCD patients in the orbitofrontal cortex, caudate nucleus, and anterior caudal and cingulate medial prefrontal cortex (Graybiel and Rauch 2000). Additionally, OCD patients have elevated activity at rest in the basal ganglia (Graybiel and Rauch 2000).

In general, there are two leading theories regarding the biochemical mechanism of OCD. The serotonin hypothesis arose about 50 years ago when it was noted that serotonin reuptake inhibitors had anti-obsessional properties (Pauls et al 2002). While there is evidence that serotonin dysfunction may play a role in OCD, 40% of patients receiving selective serotonin reuptake inhibitor (SSRI) treatment do not show clinical improvement (Pauls et al 2002). Therefore, it has been suggested that only half of the variability in OCD can be accounted for by dysfunction of the serotonergic system (Pauls et al 2002).

The alternative to the serotonin hypothesis is the dopamine hypothesis, which applies specifically to those forms of OCD related to tic disorders (especially Tourette syndrome), schizotypal personality, or poor insight (Pauls et al 2002). For example, there is evidence that Tourette syndrome is linked to dopamine dysfunction, and a majority of patients with comorbid OCD and tic disorder respond better to dopamine or dopamine/serotonin treatment than to serotonin treatment alone (Pauls et al 2002). Because the serotonin and dopamine systems are closely linked, it is possible that both systems are involved in OCD pathogenesis, an idea supported by cases of *de novo* OCD that arise in patients being treated for other conditions with antipsychotics with combined dopamine and serotonin reuptake effects (Pauls et al 2002).

Translational Approaches and Experimental Models

The use of animal models in biological psychiatry has become an important direction of research (Kalueff et al 2007e; Warnick and Sufka 2008). With high construct, predictive, and face validity, animal models allow the testing of etiologic and physiological theories of brain disorders (Korff and Harvey 2006). Ethological models became particularly useful for the neurobiological mechanisms of OCD. While some symptoms of OCD cannot be directly observed in animal models (e.g., cognitive obsessions), many repetitive human behaviors are translatable into animal phenotypes (Table 1). For example, tail chasing, weaving, fur chewing, excessive grooming, cleaning, pecking, food restriction-induced hyperactivity, reward alternation, excessive lever pressing, barbering, marble burying, acral lick dermatitis, and feather plucking, can be either categorized as naturally occurring repetitive stereotypic behaviors, or instinctive stress-induced motor behaviors (Korff and Harvey 2006).

Other examples of OCD-like behaviors in animals may include excessive or inappropriate variations in water-drinking, attack behaviors, territorial displays, chewing, vocalizations, pacing, freezing, foraging, nest-building, or wheel-running (Altemus and Murphy 1996). Alterations of these behaviors by pharmacological agents, such as selective serotonin reuptake inhibitors (SSRIs), further supports a strong correlation between animal OCD-like behaviors and the respective human phenotypes. Several experimental models relevant to OCD have been described in the literature, and will be briefly summarized here.

Marble burying

The use of nesting material to cover potentially dangerous objects is a commonly observed behavior in mice (Joel 2006; Li et al 2006a), which was originally utilized in screens for anxiolytic drugs (Joel 2006; Korff and Harvey 2006; Li et al 2006a). Glass marbles have traditionally been used as a burial-evoking stimulus. Multiple factors have been cited for putting forward marble burying as a model of OCD. These include the observation that mice do not demonstrate avoidance

of the marbles (implying the objects do not evoke fear or anxiety), that animals do not grow habituated to their presence (suggesting that the behavior is not due to novelty, the efficacy of SSRIs in reducing burying but not locomotor behavior, and the tendency of the behavior to become excessive (Joel 2006; Korff and Harvey 2006; Li et al 2006a). It has been suggested that marble burying results from an inability to achieve a sense of task completion. This hypothesis proposes that burying begins as an appropriate investigative behavior, however, as the marbles are non-reactive and provide no stimulus to ending the investigation, the animal becomes frustrated and compulsive burying results (Joel 2006; Korff and Harvey 2006).

Barbering

Barbering, wherein a mouse plucks hair or whiskers from itself or cagemates, is a common behavior in laboratory animals (Carruthers et al 1998; DeLuca 1997; Kalueff et al 2006; Sarna et al 2000), that has been suggested as an animal model for trichotillomania (Garner et al 2004a; Garner et al 2004b; Kurien et al 2005). Similarities between barbering in mice and human trichotillomania include patterning of hair pulling around the scalp, eyes, and genitals, increased prevalence in breeding animals, female bias, pubertal onset, and genetic contribution (Garner et al 2004a).

Nest building

Nest building is an innate behavior in mice that does not require training in order to produce robust results. Nearly all mice given a gauze nestlet to shred, use the material to build round or oval nests (Li et al 2006a). Serotonin and norepinephrine uptake inhibitors, as well as GABAergic anxiolytics, have been shown to reduce nest building at doses that do not affect motor activity (Li et al 2006a). The effectiveness of these drugs, which are commonly used in the treatment of OCD patients, suggests that nest building may be a relevant model of OCD.

Grooming behavior

Care of the body surface is an innate behavior in rodents and many other animal species (Fentress 1977; Kalueff and Tuohimaa 2005; Spruijt et al 1992). In laboratory rodents, grooming has been identified as a complex patterned behavior which can be divided into distinct stages (Aldridge and Berridge 1998; Berridge 1990; Berridge and Aldridge 2000; Berridge et al 2005a; Berridge et al 1987), and which is highly sensitive to stressors, psychotropic drugs, and genetic manipulations (Kalueff et al 2007a; Kalueff and Tuohimaa 2005). Ethological analysis of grooming assesses an animal's adherence to the stereotyped grooming pattern as well as other measures including regional distribution and interruptions of grooming bouts (Berridge et al 2005b; Kalueff et al 2007a). Due to its rigid patterning and potential to become excessive, grooming has been suggested as a potential model for OCD (see Fig. 2 and (Berridge et al 2005a; Kalueff et al 2007a) for details).

Spatial alternation

In spatial alternation tasks such as the T or Y-maze, some directional preference by test rodents can be expected until the desired behavior has been sufficiently rewarded and reinforced. However, in a small percentage of cases, persistence in preference may remain despite vigorous training, which may be used as a model compulsive behavior seen in OCD patients (Tsaltas et al 2005). Interestingly, Tsaltas et al. (2005) have put forward spatial alternation as a low anxiety model for OCD which is sensitive to serotonergic manipulations commonly used in treating OCD.

Genetic Models of OCSD

As already mentioned, genetic factors also play a key role in the OCD-like pathogenesis in humans. Several lines of animal research seem to support this notion. For example, serotonin transporter (SERT) has long been implicated in human anxiety and OCD (Kalueff et al 2007d; Stengler-Wenzke et al 2004), whereas SERT knockout rodents are extensively used as genetic models of affective disorders (Holmes et al 2002; Homberg et al 2007a; Homberg et al 2007b; Homberg et al 2007c; Kalueff et al 2007b; Perona et al 2008). In several different tests, SERT

knockout mice showed greater prevalence of horizontal over vertical dimension of their exploration, and consistently displayed increased turning and meandering behavior (Kalueff et al 2007b; Kalueff et al 2007c). Interestingly, SERT knockout rats showed similar "high-turning" phenotype (Homberg, 2008, personal communication), potentially representing a common perseverance-like phenotype (Kalueff et al 2007c). In line with this, although stereotypic chewing and grooming behaviors were unaltered in SERT knockout mice (Kalueff et al 2007b), SERT knockout rats did display increased grooming behavior (Homberg, 2008, personal communication). Collectively, these observations suggest that SERT deficit in rodents may be associated with some alterations in OCD-related domain.

Similarly, serotonin 5-HT_{2C} receptor knockout mice may also be utilized as a model of OCD in animals, since these mice exhibit increased chewing and head dipping. Specifically, 5-HT_{2C} knockout mice compulsively chew non-nutritive substances, leaving significantly fewer ragged edges than control subjects (Chou-Green et al 2003). This abnormal oral behavior is complemented by "mental rigidity," manifested in a slower habituation of head dipping into a hole in the center of an elevated square board. While clinical evidence implicating the serotonin system in OCD is limited, studies reveal increased fluid levels of a serotonin metabolite 5-HIAA in the cerebral spinal fluid of OCD human patients, supporting the likelihood of a correlation between serotonin and OCD (Chou-Green et al 2003; Joel 2006).

Recent studies found that a targeted deletion of *Sapap3* (a gene encoding protein highly expressed in excitatory synapses of the striatum) induces pronounced OCD-like behaviors in mice (Welch et al 2007). *Sapap3*-mutant mice display excessive and self-injurious behaviors, including self-inflicted facial lesions. Additionally, behavioral tests in these mutants indicate significantly increased duration of grooming and a greater number of grooming bouts, even during periods of the day generally associated with sleep. This compulsive-like behavior was accompanied by an increase

in anxiety levels in the open field test and light-dark chamber. The selective expression of *Sapap3* rescues these behavioral deficits, supporting the role of excitatory transmission at cortico-striatal synapses in OCD (Welch et al 2007).

Furthermore, as the role of dopamine in OCD has been researched extensively, dopamine transporter (DAT) knockdown mice display longer grooming bouts, initiate more syntactic grooming chains, and are more likely to complete syntactic chains once started, compared to the wild type mice (Joel 2006). Hyper-dopaminergic mutant mice display significantly strengthened grooming chains which are more resistant to interruption (Berridge et al 2005b). This "sequential super-stereotypy" may translate to frequently observed rigidity in patterning and sequencing in human OCD. In fact, the basal ganglia, commonly implicated in OCD, are also thought to modulate the serial patterning of grooming chains (Joel 2006).

Further supporting the validity of grooming behavior in experimental modeling of OCD (Fig. 2), the *Hoxb8*^{lox} mutant mouse, displays a distinct persistence in grooming, inducing a longer duration of grooming, more frequent initiation of grooming, and excessive grooming of cage-mates (Greer and Capecchi 2002). The presence of disproportionate grooming, hair removal, and skin lesions in these animals suggest a parallel to human trichotillomania. In line with this, *Hoxb8*^{lox} is expressed in areas generally associated with the pathophysiology of OCD: the orbital cortex, anterior cingulate, the striatum, and the limbic system (Greer and Capecchi 2002).

Likewise, D1CT-7 transgenic mice show stereotypic non-aggressive repetition in biting and skin pulling of cage mates during grooming. D1CT models have also demonstrated evidence of abnormal digging, climbing, and tic-like behaviors (Campbell et al 2000; Korff and Harvey 2006; McGrath et al 2000). These OCD-like behaviors may be due to the expression of a neuro-potentiating cholera toxin transgene in dopamine D1 receptors in the amygdala (McGrath et al 1999).

Another recent study examined compulsive behaviors in estrogen-deficient aromatase knockout mice, focusing on several different phenotypes (Hill et al 2007). This group reported that adult male, but not female, aromatase knockout mice showed excessive barbering, grooming and wheel-running, which were normalized by chronic treatment with 17beta-estradiol. These data link estrogen status and compulsive behaviors in male animals, and may have important therapeutic implications in OCD patients (Hill et al 2007).

Conclusions

The efficacy and variety of available animal models offer great promise in future translational research in the field of biological psychiatry (Kalueff et al 2007e). While behavioral paradigms are particularly valuable in the testing of psychotropic drugs and environmental modifiers, genetic animal models further allow researchers to investigate the intricate interactions of genetic and environmental factors in OCD. Additionally, neurobiological pathways can be better dissected in mutant and transgenic models.

Collectively, these important insights will play a crucial role in developing an enhanced understanding of OCD. The complexity of the disorder, its range of symptoms, and the difficultly of interpreting clinical phenotypes emphasizes the need for accelerated translational research (Bejerot et al 2001; Heyman et al 2006; Kalueff et al 2008b; Laporte et al 2008). To this end, combining different model types may be one useful avenue of progressive research (Kalueff et al 2008a), to model more accurately relevant phenotypes such as stereotypic behaviors, reward, and perseveration.

Numerous levels of experimentation are currently underway that utilize animal models to investigate the neurochemical, physiological, behavioral, pharmacological and genetic correlates of OCD and the implications for new treatments. Such animal models have already proven to be useful in exploring the neurobiology and treatment of OCD, and further translation research in this field may extend bridges between animal and clinical phenotypes.

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Figure 1. Considered an anxiety spectrum disorder, obsessive-compulsive disorder (OCD) shows clinical heterogeneity and substantial overlap with other psychiatric disorders.

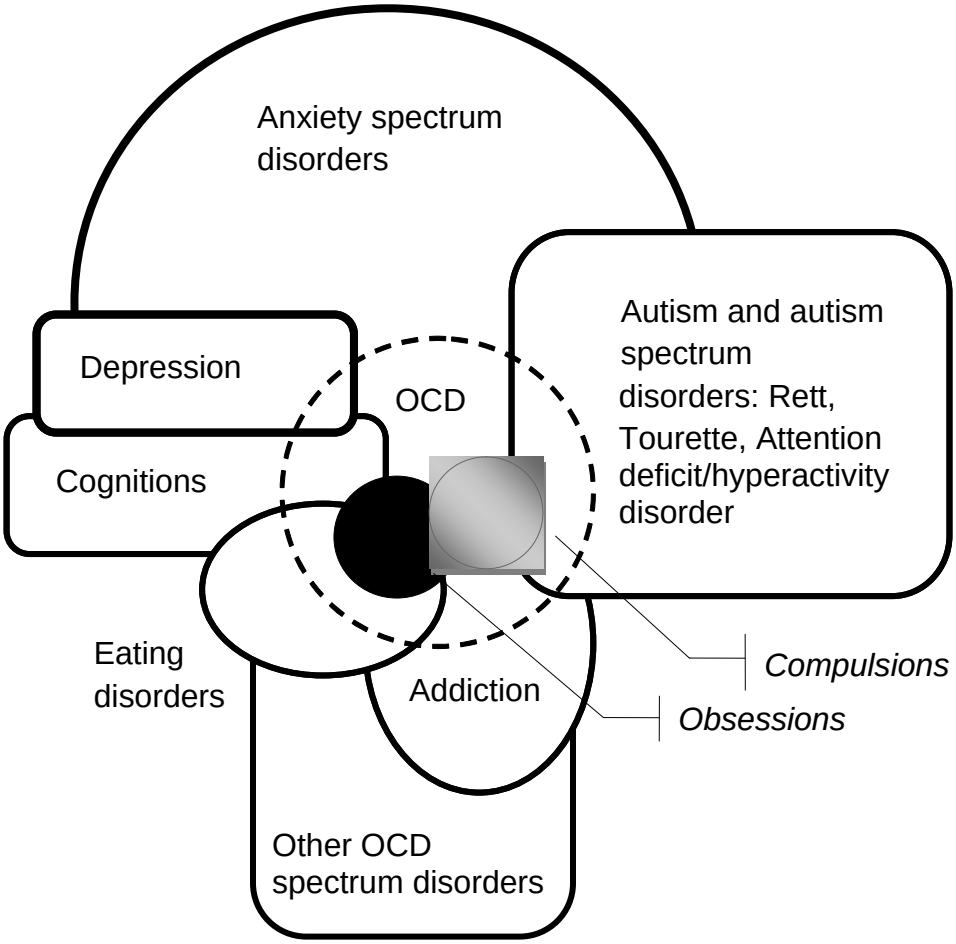

Figure 2. Potential utility of animal pathological grooming behavior as a model of human obsessive-compulsive disorder (OCD)

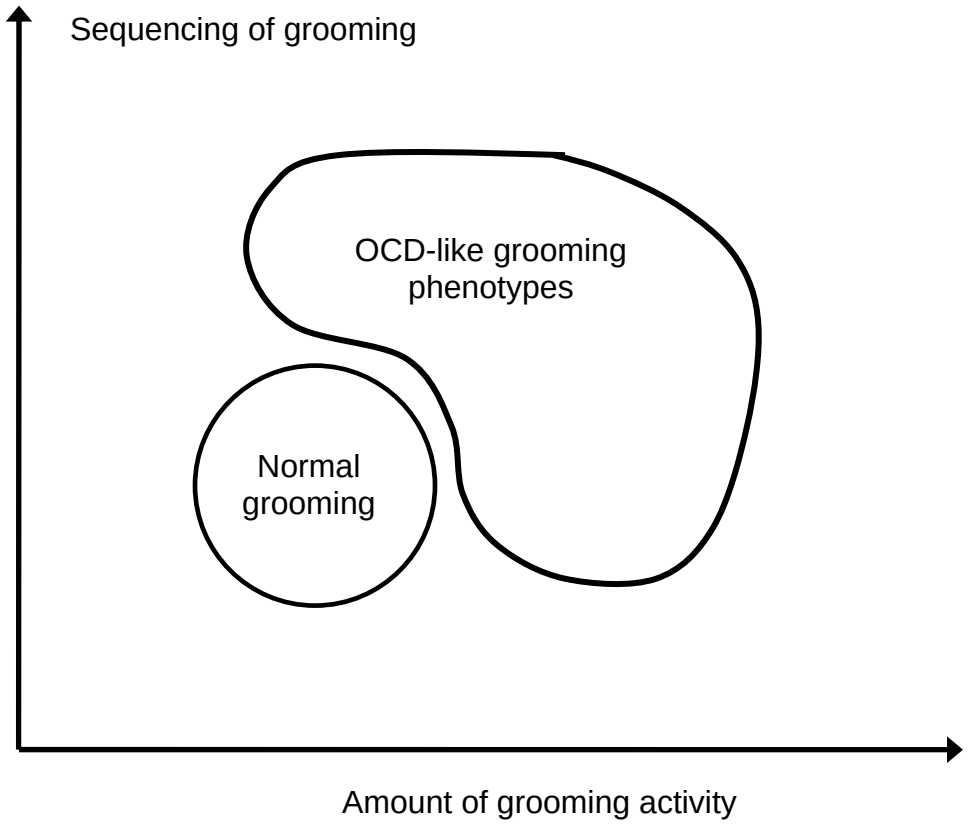

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Table 1. Parallels between some animal models and human Obsessive-Compulsive Disorder (OCD)

Types of Human OCD-like Behaviors	Relevant Animal Behavioral Phenotypes	References
Checking	Compulsive checking (Holeboard)	(Chou-Green et al 2003)
Hoarding	Aberrant nest-building, eating behaviors	(Li et al 2006b)
Washing	Aberrant grooming Barbering	(Berridge et al 2005a; Garner et al 2004b; Korff and Harvey 2006)
Ordering	Cognitive inflexibility	(Tsaltas et al 2005)